Remarks

Informalities

Claims 33 and 34 have been amended to insert a "so" before "that", as suggested by the examiner.

Rejection Under 35 U.S.C. § 103

Claims 14-16 and 33 were rejected under 35 U.S.C. § 103(a) as obvious over U.S. Patent No. 5,370,681 to Herweck et. al. ("Herweck") in view of U.S. Patent No. 5,171,264 to Merrill ("Merrill"). Claim 17 was rejected under 35 U.S.C. § 103(a) as obvious over Herweck in view of Merrill, and further in view of U.S. Patent No. 5,522,895 to Mikos *et al.* ("Mikos"). The applicants respectfully traverse these rejections.

The claimed invention

Claims 14-17 and 33 define a method for growing eukaryotic cells on a biocompatible substrate; with biocompatible polymeric tethers, and growth effector molecules, where the tethers are coupled to the substrate by the same linkers as the tethers are coupled to the growth effector molecules, the tethers prevent the internalization of the growth effector molecules, and the growth effector molecules are present in a concentration effective to enhance the rate of cell growth. Claims 32 and 34 define a method for testing a compound for an effect on the cells on the substrate of claim 33.

Claims 14-16 and 33 further require the attachment agent to be one of cyanogen bromide, succinimide, aldehyde, tosyl chloride, avidin-biotin, epoxide, and maleimide, or carbodiimide.

Herweck

Herweck discloses implantable devices for sustained release of a bioactive material, such as a therapeutic agent, a cell type, or a diagnostic agent, into a fluid flow pathway of a patient (see column 3, lines 14-16 and 30-37). Herweck discloses first coating or modifying the surface with glycoproteins such as fibronectin prior to seeding the device with cells (see column 4, lines 62-68). Herweck discloses that such coating may result in improved adhesion of cells (see column 6, lines 23-29). As recognized by the Examiner, Herweck does not disclose or suggest the use of a tether attaching a growth effector molecule to a substrate but merely coats, or adsorbs, the factor upon the substrate. More importantly, Herweck **does not describe or provide the motivation to lead one of ordinary skill in the art to growing cells** by maintaining the cells in contact with the composition defined therein which comprising a tether attaching a growth effector molecule to a substrate without causing internalization of the effector molecule by the cells.

Herweck describes a polylumenal implantable device comprising a body defining a plurality of capillary lumina which is suitable for use as an arterial or venous bypass or shunt or intra-organ implant, etc. (col. 3, lines 24-37). A device comprising a plurality of capillary lumina suitable for use as an arterial or venous bypass would require the plurality of capillary lumina to be free from clogging, and one of ordinary skill in the art would recognize that stimulation of cell growth within the plurality of capillary lumina would result in clogging of the capillary lumina, therefore defeating the very purpose of the device described in Herweck.

In summary, there is no recognition of the critical concentration of growth effector molecules, the need for a tether that allows the growth effector molecules to enhance the rate of growth without internalization of the growth effector molecules, nor the role the tethers and linkers play in such a substrate.

Merrill

Merrill discloses star molecules of polyethyleneoxide (PEO) that are biocompatible and demonstrate non-thrombogenic properties. Merrill discloses star molecules that could be useful in Applicants' methods, as discussed in the specification at page 7, lines 3-20. Merrill teaches that the star PEO molecules can be attached to an appropriate support surface to reduce thrombosis, to assist in protein purifications, and other proposed activities.

Merrill teaches that the composition described therein "can be used as a tool for separating and purifying biological molecules..." In addition, Merrill teaches that the PEO star molecule hydrogels described therein are **non-thrombogenic, making them suitable for applications such as intravenous catheters and implantable vascular prostheses** (col. 2, lines 17-23). Therefore, like Herweck, Merrill contemplates using the PEO star molecules described therein for application in which cell growth is undesirable. Therefore, Merrill arguably teaches away from the defined method.

Merrill does not describe using PEO molecules as tethers for attaching growth effector molecules; the requirement for a critical concentration of growth factors to enhance growth; the

requirement for tethers which allow the growth factors to bind to cells but which prevent internalization, nor the role linkers play.

The combination of Herweck and Merrill

The prior art does not disclose each of the claimed elements.

The prior art does not teach one of ordinary skill in the art to modify the prior art as applicants have done, to achieve the claimed methods. The goals of the prior art are different: Herweck is drawn to drug delivery; Merrill is drawn to devices for use in bioseparations. Neither reference relates to materials for culturing cells. One skilled in the art would not normally look to art relating to drug delivery or bioseparations for guidance on ways to increase the rate of cell growth in culture. Even if one did, Herweck does not suggest that it would be advantageous to tether growth factors to the substrate, and Merrill does not suggest using the star molecules for tethering growth effector molecules to a substrate. Therefore, Herweck and Merrill in combination do not teach or motivate one of ordinary skill in the art to make and use a composition comprising a growth effector tethered to a substrate surface.

Accordingly, Herweck and Merrill, combined, would not lead one of ordinary skill in the art to make and use a composition as defined in the claims for stimulating cell growth; nor would Herweck and Merrill, combined, would lead one of ordinary skill in the art to have a reasonable expectation of the method defined in the claims. Therefore, claims 14-16 and 33 are not *prima facie* obvious over Herweck in view of Merrill ((*see*, *Hodosh v. Block Drug Co., Inc.*, 786 F.2d 1136, 1143 n.5, 229 USPQ 182, 187 n.5 (Fed. Cir. 1986); *see also* MPEP § 2141).

Herweck or Merrill in combination with Mikos

Claim 17 was rejected over Herweck in view of Merrill, and further in view of Mikos. Claim 17 further defines the polymer of claim 16 as biodegradable. Therefore, the discussion above is fully applicable to the rejection of claim 17 as obvious over Herweck in view of Merrill. Accordingly, Herweck in view of Merrill would not make obvious claim 17.

Mikos describes a biodegradable polymeric matrix which can be seeded with cells and implanted. In particular, Mikos describes a biodegradable, bioresorbable, three-dimensional template for repair and replacement of diseased or injured bone (col. 2, lines 10-57). As discussed above, Herweck and Merrill describe devices as drug delivery and cell separation devices where cell growth does not occur or is undesirable. In contrast, Mikos describes a template for repair and replacement of diseased or injured bone, where cell growth is desirable. There is nothing that would lead one to combine the materials of Mikos with the devices of either Herweck or Merrill. Even if Herweck/Merrill and Mikos were combined, Mikos does not disclose or make obvious selecting growth effector molecules, determining the amount required to enhance growth rate when not internalized, chemically coupling the molecules to the substrate in a density and with appropriate linkers to result in enhanced growth rates of attached cells. Mikos does not disclose the elements missing from the Herweck/ Merrill combination. Therefore, claim 17 is not obvious over Herweck in view of Merrill and further in view of Mikos (*see, Hodosh v. Block Drug Co., Inc.*, 786 F.2d at 1143 n.5, 229 USPQ at 187 n.5; *see also* MPEP § 2141).

Double patenting

Claims 14-17 and 33 were rejected under the judicially created doctrine of obviousness-type double patenting as unpatentable over claims 1-4 of U.S. Patent No. 5,906,828 ("the '828 patent") and further in view of U.S. Patent No. 4,954,637 to Nitecki et al. ("Nitecki"), U.S. Patent No. 5,508,164 to Kausch et al., ("Kausch") and the applicants' alleged admissions. Claims 32 and 34 were rejected under the judicially created doctrine of obviousness-type double patenting over claim 20 of U.S. Patent No. 6,045,818 ("the '818 patent") and further in view of U.S. Patent No. 4,954,637 to Nitecki et al. ("Nitecki"), U.S. Patent No. 5,508,164 to Kausch et al., ("Kausch") and the applicants' alleged admissions. Applicants respectfully traverse the rejections.

Claims 1-4 of the '818 patent define a method of growing eukaryotic cells:

1. A method for growing eukaryotic cells comprising

(a) bringing into contact the cells and a composition comprising

a biocompatible solid substrate,

biocompatible branched water soluble polymeric tethers, and

growth effector molecules,

wherein one end of each tether is covalently linked to the substrate, each tether is able to covalently link more than one growth effector molecule, each growth effector molecule is covalently linked to a distal end of a tether so that the growth effector molecule cannot be internalized by cells attached to the substrate, and

the growth effector molecules are attached to the substrate in a concentration effective to enhance the rate of target cell growth over the rate of target cell growth with soluble growth effector molecules and growth effector molecules adsorbed to a substrate, without internalization of the molecules; and

(b) maintaining the contacting cells and composition under conditions and for a time sufficient to cause the cells to grow;

wherein the step of bringing into contact comprises administering the composition to a patient in need of cell growth.

The difference between the claims in the '828 patent and the claims in this patent is that the claims in this case recite that the tethers must be coupled to the substrate by the same linker as the tether is coupled to the growth effector molecules.

Claim 20 of the '818 patent defines a method of testing a compound for an effect on tissue.

20. A method of testing a compound for an effect on tissue comprising

(a) bringing into contact the compound to be tested and a composition comprising

a biocompatible solid substrate,

biocompatible branched water soluble polymeric tethers comprising a polymeric material selected from the group consisting of polyethylene oxide, polyvinyl alcohol, polyhydroxyalkyl (meth)acrylate, polyacrylamide, and starches,

growth effector molecules, and

growing cells,

wherein one end of each tether is covalently linked to the substrate, each tether is able to covalently link more than one growth effector molecule, each growth effector molecule is covalently linked to a distal end of a tether so that the growth effector molecule cannot be internalized by cells attached to the substrate, the growth effector molecules are attached to the substrate in a concentration effective to enhance the rate of target cell growth over the rate of target cell growth with soluble growth effector molecules and growth effector molecules adsorbed to a substrate, without internalization of the molecules, and

wherein the growing cells are bound to the growth effector molecules;

(b) incubating the compound and the composition under conditions promoting cell growth; and

(c) observing the cells for any effect not observed in cells not brought into contact with the composition,

wherein the substrate is selected from the group consisting of glasses, metals, polystyrenes, polyethylene vinyl acetates, polypropylenes, polymethacrylates, polyacrylates, polyethylenes, polyethylene oxides, polysilicates, polycarbonates, polytetrafluoroethylene, fluorocarbons, nylon, silicon rubber, polyanhydrides, polyglycolic acids, polyhydroxyacids, polyesters, polycapralactone, polyhydroxybutyrate, polyphosphazenes, polyorthoesters, polyurethanes, and combinations thereof .

There are two differences between the claims in this application and the claims in the '818 patent:

The selection of the linker between the tether and the substrate and the tether and the growth effector molecules, and the selection of the multi-branched tethers.

The issue with respect to obviousness-type double patenting is whether these differences are obvious from the claims in the '828 and '818 patents.

As WO 89/05616 by Bio-Metric Systems, Inc. (previously cited by the Examiner) clearly indicates, the nature of the linking agent plays an important function in directing the orientation and spacing of the tether and the attached growth effector molecules, which is important for obtaining a substantially optimum activity of the growth effector molecule (see, for example, p. 14, lines 1-19 of WO 89/05616). Claims 1-4 of the '828 patent and claim 20 of the '818 patent neither recite nor make obvious this important feature.

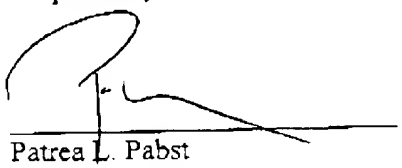
The Examiner conceded in the office action mailed on March 31, 2003, that the nature of the linking agent plays an important function in directing the orientation and spacing of the tether and the attached growth effector molecule, which is important for obtaining a substantially optimum activity of the growth effector molecule. In the office action mailed on June 10, 2003, the Examiner further conceded that both the '828 and the '818 patents do not recite using the same attachment agent to link the tether to the substrate and the growth effector molecule. Therefore, according to the Examiner's own statements, claims 1-4 of the '828 patent would not render obvious claims 14-17 and 33 because claims 1-4 of the '828 patent fail to recite an

important feature of claims 14-17 and 33, the attachment agent. Similarly, claim 20 of the '818 patent would not make obvious claims 32 and 34.

The Examiner further alleged that claims 14-17 and 33 are obvious over claims 1-4 of the '828 patent further in view of Nitecki, Kausch, and the specification of the present application. The applicants respectfully submit that this obviousness type double patenting is improper. As described in MPEP, § 804(III), a double patenting rejection differs from an obviousness rejection based on prior art in that it **must rely on a comparison with the claims in an issued or to be issued patent** (see *In re Barfeld*, 925 F.2d 1450, 17 USPQ2d 1885 (Fed. Cir. 1991). Here, the Examiner based the obviousness type double patenting not on claims 1-4 of the '828 patent alone, but rather, on claims 1-4 of the '828 in combination with Nitecki, Kausch, and the specification of the present application. The rejection is therefore improper. For the same reason, rejection of claims 32 and 34 under the judicially created obviousness type double patenting over claim 20 of the '818 patent in combination with Nitecki, Kausch, and the specification of the present application is clearly improper.

Allowance of claims 14-17 and 32-34 is respectfully solicited.

Respectfully submitted,



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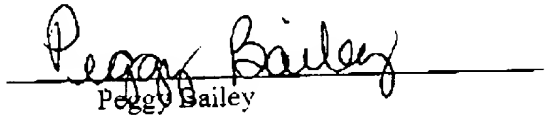
CERTIFICATE OF FACSIMILE TRANSMISSION

I hereby certify that the enclosed Response to Office Action and all documents shown as being attached is being facsimile transmitted to Mail Stop Non-Fee Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date shown below.

Date: August 27, 2003



Peggy Bailey

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